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REVIEW

Is cardiac resynchronization therapy an option in heart failure patients with preserved ejection fraction? Justification for the ongoing KaRen project

La stimulation cardiaque de resynchronisation est-elle une option thérapeutique dans l'insuffisance cardiaque à fraction d'éjection préservée? Justification pour l'étude KaRen

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Received 1st November 2009; received in revised form 23 January 2010; accepted 25 January 2010

Available online 23 June 2010

KEYWORDS

Heart failure;
Preserved ejection
fraction;
Diastolic dysfunction;
Dyssynchrony;
Echocardiography

Summary The relevance of electrical and mechanical dyssynchrony has been demonstrated in heart failure with reduced ejection fraction. Preserved ejection fraction is present in as many as 50% of patients with chronic heart failure. Recent small studies suggest that both electrical and mechanical left ventricular dyssynchrony are sometimes present in patients with heart failure and preserved ejection fraction (HFPEF). These data remain controversial and a robust validation of this hypothesis has to be achieved. In the present paper, we review in detail the concepts and try to justify the ongoing KaRen registry. This is a prospective, multicentre, international, observational study to characterize the prevalence of electrical or mechanical dyssynchrony in HFPEF and the resultant effect on prognosis. Patients are enrolled currently at the time of an acute congestive episode. The diagnosis of HFPEF is made according to clinical data, natriuretic peptides and echocardiography for the measurement of ejection fraction. Once stabilized, patients return for a hospital check-up. They undergo clinical and biological evaluation, electrocardiography and Doppler echocardiography. Thereafter, patients are followed every six months, for at least 18 months for mortality, and heart failure-related and non-cardiovascular hospitalizations. KaRen aims to characterize electrical and mechanical dyssynchrony and to

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MOTS CLÉS

Insuffisance
cardiaque ;
Fraction d'éjection
préservée ;
Dysfonction
diastolique ;
Asynchronisme ;
Échocardiographie

assess its prognostic impact in HFPEF. The results may improve our understanding of HFPEF and generate answers to the question of whether or not dyssynchrony could be a target for cardiac resynchronization therapy in HFPEF.

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Résumé L'importance de l'asynchronisme électrique et mécanique a été largement démontrée chez les patients insuffisants cardiaques systoliques. L'insuffisance cardiaque à fraction d'éjection préservée représente actuellement près de 50 % de l'ensemble de la population des insuffisants cardiaques. De récentes petites études ont suggéré qu'un certain degré d'asynchronisme électrique et ou mécanique pouvait être observé chez les patients insuffisants cardiaques à fraction d'éjection préservée. Ces données restent controversées et une large étude prospective restait ainsi nécessaire pour confirmer ou non l'hypothèse d'un rôle de l'asynchronisme dans la physiopathologie de cette maladie mal comprise qu'est l'insuffisance cardiaque à fraction d'éjection préservée. C'est la raison pour laquelle, l'observatoire franco-suédois KaRen a été initié. Celui-ci est donc prospectif, multicentrique et vise à décrire une population d'insuffisants cardiaques à fraction d'éjection préservée en particulier, en termes d'asynchronisme (électrique et mécanique) mais aussi en termes pronostique. Les patients sont inclus lorsqu'ils sont vus pour un épisode congestif, puis sont réévalués quatre à huit semaines plus tard en termes clinique, biologique, électro- et échocardiographique. Le diagnostic de cette insuffisance cardiaque à fraction d'éjection préservée reste difficile et dans KaRen, outre la clinique et la fraction d'éjection, il a été ajouté un seuil de peptique natriurétique pour retenir ou non le diagnostic. Ces patients sont revus à quatre à huit semaines après traitement et suivis par téléphone tous les six mois, pendant 18 mois. Nous allons ainsi étudier prospectivement la prévalence et la signification pronostique de l'asynchronisme, en particulier échocardiographique et ce, en utilisant un protocole strict et des modalités d'analyse actuelles. Nous devrions donc être en mesure, à partir du suivi prospectif de 400 patients, capable de mieux comprendre cette maladie et connaître l'importance de l'asynchronisme dans sa physiopathologie et peut-être son traitement.

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Abbreviations

CHF	Congestive heart failure
CRT	Cardiac resynchronization therapy
DHF	Diastolic heart failure
EF	Ejection fraction
HF	Heart failure
HFPEF	Heart failure with preserved ejection fraction
LV	Left ventricular
SHF	Systolic heart failure

Background

Electrical and mechanical dyssynchrony are common in patients with HF and depressed (inferior to 40%) EF. However, as many as 50% of patients with chronic HF have what is now called HFPEF. Patients with signs and symptoms of HFPEF (EF \geq 50%), but not those with restrictive, DHF, will be studied in the KaRen multicentre study, looking at prognosis and electrical and mechanical dyssynchrony (using electrocardiography and echocardiography performed according to a stringent protocol and reviewed in a dedicated core laboratory) [1–9]. Recent small studies suggest that LV dyssynchrony might exist in patients with HFPEF [10–14].

Electrical and mechanical dyssynchrony in HF with depressed EF are known to be harmful [15,16], but we do not have such information regarding HFPEF. Further studies

are therefore necessary. But we also need to use a precise definition of HFPEF, which is not merely a diagnosis made on the basis of the presence of symptoms and preserved EF [17–19]. We need to ensure that the diagnosis (elevated filling pressure) is in accordance with the guidelines [20]. In line with these principles, KaRen is an ongoing registry looking at the prevalence and prognostic impact of dyssynchrony in HFPEF [1].

We designed KaRen as a prospective, multicentre, international, observational study to characterize HFPEF and determine whether electrical or mechanical dyssynchrony affects prognosis. We are looking at HF-related and non-cardiovascular hospitalizations over a follow-up time of 18 months.

Elements of heart failure with preserved ejection fraction

CHF affects about 2% of the western population, with prevalence increasing sharply from 1% in those aged 50 years to 10% in those aged over 75 years [4,7]. It is the most common cause of hospitalization in patients aged over 65 years [4,21]. CHF is defined as a syndrome characterized by an impaired ability of the heart to fill with and/or eject blood, resulting in a classical constellation of signs and symptoms [3].

HFPEF is being recognized increasingly as a pathophysiological entity [4]. The proportion of patients with HFPEF is about 50% in studies of the general HF population [21–24]. These patients were previously classified as having DHF or HFPEF. However, DHF has its own definition and may not be strictly identical to HFPEF [4,5,23]. HFPEF can be defined as follows:

- an EF superior or equal to 45%, superior or equal to 50%, or superior or equal to 55% [4];
- the presence of clinical signs and symptoms of HF, according to the Framingham criteria [25];
- objective signs of congestion or elevated filling pressure (natriuretic peptides, invasive haemodynamics, echocardiography) [20] in the absence of acute ischaemia, severe valvular disease or other severe medical condition that explains the congestion.

As the specificity of signs and symptoms of congestion in elderly patients is debatable, the clinical evaluation is being corroborated systematically by the level of brain natriuretic peptide or N-terminal prohormone brain natriuretic peptide in the KaRen study [1]. Furthermore, echocardiography should be performed before inclusion, which should be able to verify the diagnosis [1].

The prognosis of HFPEF in epidemiological surveys is nearly as poor as that of SHF, but in therapeutic clinical trials of HFPEF (PEP-CHF, CHARM-Preserved and I-PRESERVE), the prognosis was much better than in clinical trials of SHF patients [18,19]. In I-PRESERVE, during a mean follow-up of 49.5 months, the primary outcome (death from any cause or hospitalization for a cardiovascular cause [HF, myocardial infarction, unstable angina, arrhythmia or stroke]) occurred in 36.5% of patients [20]. According to a recent meta-analysis, mortality was 40.6% in the reduced LV EF group vs 32.1% in the HFPEF group after an average follow-up of 47 months [25]. The great discrepancy between registries and clinical trials might be due in part to the fact that patients were categorized as HFPEF patients essentially on the basis of signs and symptoms of HF and a preserved EF; some “HF-like syndromes” might therefore have been included. We thus need to consider objective criteria, to distinguish “true” HFPEF from “HFPEF-like syndromes”, where comorbidities might explain symptoms that are not associated with any elevation in LV filling pressures. Furthermore, the clinical trials excluded older patients and/or those with significant comorbidities. In epidemiological surveys, information on cause of death is not available and may well have been non-cardiovascular.

Recently, Henkel et al. published complementary results. They found that HFPEF patients have less cardiovascular disease before death and are less likely to experience cardiovascular death than those with reduced EF, and that the proportion of cardiovascular deaths declined over time [26]. Such observations have also been reported by Tribouilloy et al. [7]. These recent data highlight the fact that the high mortality rates observed in HFPEF and SHF may have different causes. In SHF, the main reason is HF (pump dysfunction and sudden death), whereas in HFPEF, the causes are mixed and are explained, at least in part, by comorbidities [21,26–30]. Nevertheless, we have to keep in mind that patients included in these studies may

not have actually had HFPEF. Indeed, in CHARMES, the echocardiographic sub-study of the CHARM-Preserved study, a third of patients did not have any diastolic dysfunction [31]. In addition, in clinical practice, we have observed that the elderly patients in whom we diagnose HFPEF are hospitalized repeatedly for congestion (that is cardiovascular in origin most of the time) before dying. Under these circumstances, they need diuretics and blood pressure control [23,31]. Hence, we certainly have to improve their treatment to decrease their cardiovascular morbidity [30].

Why look for dyssynchrony in heart failure with preserved ejection fraction?

The prognostic importance of conduction disturbances (left bundle branch block) in the progression and severity of SHF has been established; this is not the case in HFPEF [16]. The prevalence of left bundle branch block is 25% in SHF and 8.1 or 14% according to the I-PRESERVE and CHARM-Preserved studies, respectively [32]. Indeed, in the CHARM-Preserved population, left bundle branch block had a modest, or possibly no predictive impact on cardiovascular death or hospitalization for HF, after a mean follow-up of 38 months [33]. In addition, no effect of left bundle branch block on prognosis was observed in the French epidemiology study performed by Tribouilloy et al. [34].

According to Brutsaert, chronic HF might be seen as a single, pathophysiological entity encompassing a continuous spectrum of closely related phenotypes. Age, hypertension, diabetes, being overweight and female have been associated with the HFPEF phenotype [35]. These characteristics have been shown to modify the process of LV remodelling and hypertrophy without preventing it. Also, haemodynamic overload, neurohormonal imbalances, endothelial dysfunction, cytokines and even the mean collagen volume fraction (a measure of myocardial fibrosis) have been reported to be similar in HFPEF and SHF [36,37]. It appears relevant, then, to explore specifically the prevalence and consequence of dyssynchrony in patients who develop the HFPEF phenotype [4,33–37].

Recent studies on CRT indicate that early treatment of dyssynchrony might be beneficial [38]. The REVERSE study (which included 610 SHF patients with New York Heart Association class I or II symptoms and a broad QRS complex) demonstrated significant improvement in LV end-systolic volume in the group of patients treated with CRT (-18.4 mL/m^2 vs -1.3 mL/m^2 ; $p < 0.0001$), accompanied by a reduced need for HF-related hospitalization in the 262 European patients followed for 24 months [38,39]. These results were corroborated in the MADIT-CRT study, designed as a morbidity and mortality trial, which included 1820 patients with New York Heart Association class I or II symptoms, LV EF inferior or equal to 30% and QRS superior or equal to 130 ms [40]. Also, non-randomized studies have yielded limited but encouraging results in SHF with QRS inferior to 120 ms but with mechanical dyssynchrony [41,42]. The RethinQ trial did not confirm the beneficial effect of CRT when only mechanical dyssynchrony was found, according to the criteria in that study [43,44].

Mechanical dyssynchrony assessment

Ventricular dyssynchrony in SHF is frequent and portends a worse outcome [45]. Electrical dyssynchrony, as indicated by prolonged QRS duration (≥ 120 ms) and/or left bundle branch block, is present in approximately 30% of patients [45]. In HFPEF, according to small monocentric studies, the prevalence of electrical and/or mechanical dyssynchrony during systole and/or diastole ranges from 10 to 60% [13,14,43–46]. With regard to the assessment of mechanical dyssynchrony, despite a large number of mechanistic and multicentre studies, only electrical dyssynchrony in SHF is considered for treatment (QRS > 120 ms, indication for CRT) [47]. The assessment of mechanical dyssynchrony remains non-consensual, operator-dependent but is also dependent on haemodynamics or echocardiography. Nevertheless, past studies and new imaging techniques are providing new knowledge of the physiopathology of mechanical dyssynchrony and new tools for its assessment. The recently started Echo-CRT trial is also helping the aim of characterizing mechanical dyssynchrony through a multicentre study [48–51]. We therefore decided to evaluate the prognostic significance of QRS prolongation and mechanical dyssynchrony variables in patients with HFPEF.

In the past ten years, many studies of mechanical dyssynchrony and its assessment have been performed. QRS width is correlated with prognosis, and concordant studies, even in a narrow QRS population with LV EF inferior to 40%, have demonstrated the prognostic value of interventricular and intra-LV dyssynchrony [48].

As pointed out by Brutsaert and Sys many years ago, ventricular relaxation and contraction are part of a continuous cycle, and HF with altered or preserved EF might somehow be considered to be two expressions of the same disease [52–54]. Thus, if dyssynchrony is now recognized as a very important factor in SHF, the data that we have with regard to HFPEF are sparse. De Sutter et al. found that, in 60 patients with HF and an LV EF superior to 40%, the prevalence of systolic intraventricular dyssynchrony measured by pulse tissue Doppler was 18% compared with 36% in those with a low LV EF. However, in patients with HFPEF and a QRS duration superior to 120 ms, the prevalence of intraventricular dyssynchrony in systole was the same in both HF with depressed EF and in HFPEF [46]. Wang et al., studying 60 HFPEF patients with tissue Doppler tools, found that 58% had dyssynchrony in diastole (defined as the onset and not peak E') and 33% in systole (considering the peak S') [13]. Another study with a very closed design showed that in 92 HFPEF patients, diastolic intra-LV dyssynchrony was found in 56% of the population and systolic inter-LV dyssynchrony in 33% of the population [55]. The prevalence of mechanical dyssynchrony was quite high but less than that observed in systolic CHF (57% in systole and 43% in diastole). Twenty-five percent of the HFPEF patients had isolated systolic dyssynchrony and the relationship between systolic and diastolic dyssynchrony was poor.

Most patients with HFPEF have hypertension, but few observational studies have focused on the prevalence of mechanical dyssynchrony in hypertensive patients, comparing patients with diastolic dysfunction, high natriuretic peptide levels or exercise limitations. The results appear quite homogeneous. These studies used tissue Doppler imag-

Table 1 Key exclusion criteria for patients in the KaRen study.

1	Evidence of primary hypertrophic or restrictive cardiomyopathy, or systemic illness known to be associated with infiltrative heart disease
2	Known cause of right heart failure not related to left ventricular dysfunction
3	Pericardial constriction
4	Clinically significant pulmonary disease, as evidenced by current requirement for home oxygen
5	End-stage renal disease currently requiring dialysis
6	Bi-ventricular pacemaker (CRT); patients who have a conventional pacemaker may be included
7	Anticipated or indication for cardiac surgery; patients who have indication for surgery, but may not undergo surgery because of some contraindication (e.g. age), may NOT be included
8	Anticipated percutaneous intervention on aortic stenosis; patients who undergo other percutaneous intervention, for example PCI, may be included

CRT: cardiac resynchronization therapy; PCI: percutaneous coronary intervention.

ing to look for dyssynchrony and none of them followed the patients to assess the impact of their findings on prognosis. LV dyssynchrony seems to be common among hypertensive patients but particularly those with LV hypertrophy [2,56]. The severity of LV systolic dyssynchrony seems then to be related to the magnitude of LV hypertrophy. With regard to diastolic dyssynchrony (assessed using the time to peak E', by analogy to what is done for S' using tissue Doppler imaging), the results are more confused, with no correlation between diastolic dyssynchrony and diastolic pattern, and no correlation between systolic and diastolic dyssynchrony [2,11,45,56].

KaRen was thus designed to study incidence and prognostic impact of mechanical (systolic and diastolic) and

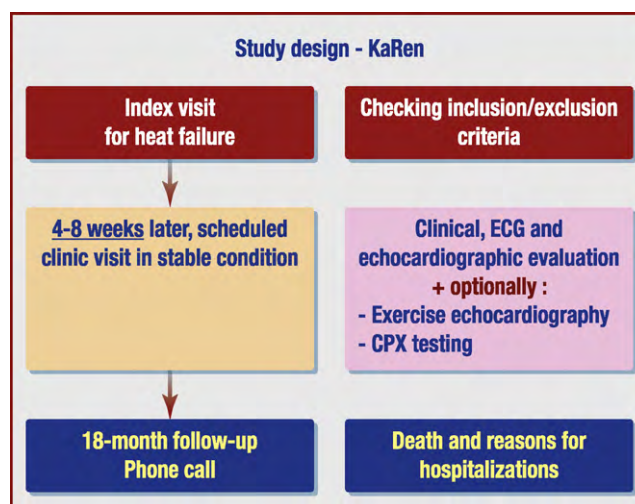


Figure 1. KaRen study design. CPX: cardiopulmonary exercise testing.

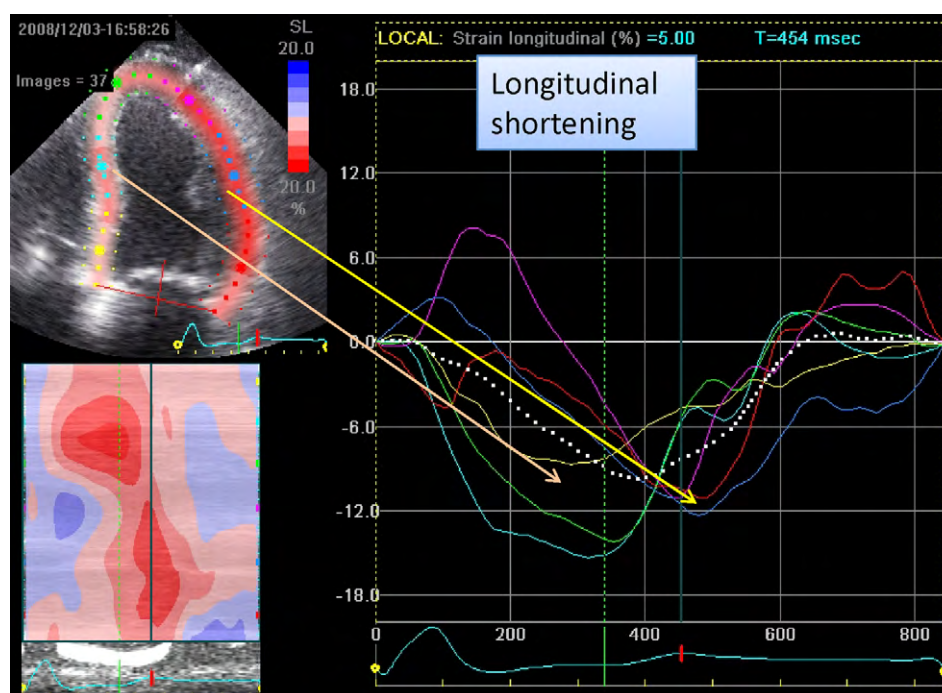


Figure 2. Example of a KaRen patient with heart failure with preserved ejection fraction and significant mechanical dyssynchrony. We present here an assessment of longitudinal dyssynchrony using two-dimensional strain capabilities.

electrical dyssynchrony in a characterized population of HFPEF. Patients will be examined by echocardiography after treatment of the congestion (Table 1, Fig. 1). We will not focus only on the echocardiographic tools used in PROSPECT and RethinQ to assess mechanical dyssynchrony [43,57]. We will use a multiparametric approach and new treatment of the echocardiographic images, especially the two-dimensional speckle tracking strain analysis technique proposed recently as being more reproducible and relevant for measuring mechanical dyssynchrony in the longitudinal direction but also in the radial or circumferential directions [58–62]. Our assessment of electrical and mechanical dyssynchrony will be centralized in core laboratories (echocardiography in Rennes, France and electrocardiography in Stockholm, Sweden) and mechanical dyssynchrony will always be assessed using the same echocardiograph machine and according to optimal stringency with regard to the technique of image acquisition and analysis (Fig. 2). Furthermore, in a subset of patients (a predefined sub-study), we will assess mechanical dyssynchrony at the time of congestion and afterwards, when the patient has been treated optimally (and the overload controlled). KaRen should then be able to verify the existence of mechanical dyssynchrony in some patients diagnosed with HFPEF, but the study will also provide an assessment of the robustness of the diagnosis of HFPEF and whether associated mechanical dyssynchrony is influenced by load modifications [63].

Conclusion

The KaRen study is being conducted to provide answers to two principal questions. What is the prevalence of electrical and/or mechanical dyssynchrony in the HFPEF population? How do electrical and mechanical dyssynchrony correlate

with outcome as assessed by a combined endpoint of all-cause death or HF hospitalization at 18-month follow-up? This prospective, observational study also aims to assess the potential usefulness of conducting clinical trials on CRT in patients with HFPEF.

Conflict of interest statement

None.

Funding

This work is supported by a research grant from Medtronic Europe.

Acknowledgements

We wish to thank the French Society of Cardiology, the French Federation of Cardiology and the Swedish Heart and Lung Foundation for their support. We would also like to thank Medtronic Europe for their research grant. Finally, we wish to express our gratitude to all the co-investigators (Magnus Edner, Stéphane Lafitte, Hans Persson, Fabrice Bauer, John Öhrvik, Pierre-Vladimir Ennezat, Camilla Hage, Ida Löfman, Yves Juilliere, Damien Logeart, Geneviève Derumeaux, Pascal Gueret, Pascal Lim, Jean-Noel Trochu, Nicolas Piriou, Gilbert Habib, François Tournoux, Patricia Réant, Christine Selton-Suty, Cyrille Bergerot, Catherine Sportouch) and to the *Service de cardiologie* in Rennes, especially Marie Guinoiseau, Valérie Le Moal, Christian de Place, Romain Ollivier, Cécile Hamon, Jean-Claude Daubert, Christophe Leclercq and Philippe Mabo.

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